(19) **European Patent Office**

(11) Publication Number: **0 312 087 A2**

(12) # EUROPEAN PATENT REGISTRATION

(21) Registration Number: 88117117.7

(51) Int. Cl.: **C07H 15/04**

(22) Application Date: 10/14/88

(30) Priority: **10/14/87 DE 3734853**

(43) Publication Date of Application:
04/19/89 Patent Form 89/16

(84) Destination Countries Stated:
AT BE CH DE ES FR GB FR IT LI LU NL SE

(71) Applicant: **LUITPOLD WERK**
Chemisch-pharmazeutische Fabrik GmbH & Co.
Postfach 70 12 08
D-8000 Munich 70 (DE)

(72) Inventor: **Meinetsberger, Elke, Dr. rer. nat.**
Friedenheimerstrasse 145
D-8000 Munich 21 (DE)

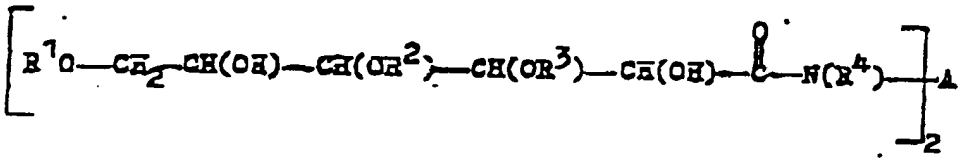
(74) Representative: **Zumstein, Fritz, Dr. et al**
Dr. F. Zumstein Dipl.-Ing., F. Klingseisen
Bräuhausstrasse 4
D-8000 Munich 2 (DE)

(54) Amides of Bis-Aldonic Acids and A Method for Their Preparation

(57) The invention concerns amides of bis-aldonic acids, in which the underlying aldonic acids can be bonded glycosidically in the 3, 4 or 6 position with a galactopyranosyl, mannopyranosyl, glucopyranosyl or oligopyranosyl radical. They are the starting products for the preparation of the corresponding polysulphuric acid esters.

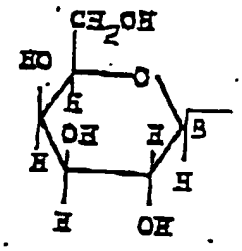
Amides of Bis-Aldonic Acids and A Method for Their Preparation

The invention concerns amides of bis-aldonic acids of the general formula I



(I)

wherein either
all radicals R^1, R^2 and R^3 represent a hydrogen atom, or
two of the radicals R^1, R^2 and R^3 represent a hydrogen atom and the third radical represents a radical of formulas II through VII,



(II)

(III)

(IV)

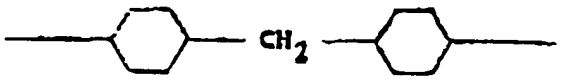
(V)

(VI)

(VIA)

m represents 0, 1, 2, 3, 4, 5 or 6,
A in formula I represents a straight chain or branched chain saturated alkylene radical with 2 to up to 22 carbon atoms that can be substituted by one or more $-CO_2R^5$ radicals and this alkylene radical can possibly be interrupted by up to 5 –0-, -S-, -S-s_, $-5(O)_n$ -,


and/or $-NR^6$ groups or cycloalkylene or arylene radicals or A represents a single bond or the radical



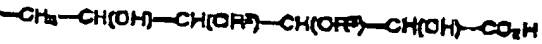
n is 1 or 2,
R^1, R^2 and R^3 simultaneously or independently from each other represent a hydrogen atom or a C_1-C_2 alkyl radical,
as well as their salts with inorganic or organic bases with the stipulation that in the case of amides of bis-gluconic acids

a) R^1, R^2, R^3 and R^4 do not simultaneously represent hydrogen atoms and that
b) if R^2 is a radical of formula II and at the same time R^1, R^3 and R^4 are hydrogen atoms in this case A is not $-(CH_2)_2-$ and that
c) if R^2 is a radical of formula IVV, wherein m = 0, 1, 3, 4 or 5, and simultaneously R^1, R^3 and R^4 are hydrogen atoms and A is an unsubstituted, straight chain alkylene radical in this case the number of chain link is an uneven number.

The invented compounds are valuable intermediate products. When reacting them with sulfating agents, highly valuable active substances with surprising pharmacological properties are obtained. Some amides of bis-aldonic acids are already known and the following literature should be pointed out:

F. Scholnick, P.E. Pfeffer, J. Dairy Sci 63 (3), 471 (1980); W.N. Emmerling, B. Pfannemüller, Starch 33 (6), 202 (1981); G. Ziegast, B. Pfannemüller, Makromol. Chem. 185, 1855 (1984); J. Masse et al., C. R. Acad. Sci., Ser. 3, 301 (1), 27 (1985); K. Dili et al. Inorg. Chim. Acta 106 (4), 203 (1985).

These familiar compounds however are nowhere described as intermediate products for the preparation of above-mentioned active substances. Emmerling and Pfannemüller used them in enzymatic syntheses with potato phosphorylase. Scholnick and Pfeffer as well as K. Dili et al. examined their chelating properties and J. Masse et al. their influence on the growth and chlorophyll content of grains.
The following explanations apply to the different substituents or radicals (as stated in the various formulas) mentioned in connection with the invention at issue:
The underlying aldonic acids in the amides of bis-aldonic acids at issue have the general formula X.


(X),

wherein R^1, R^2 and R^3 have the meaning as described. These aldonic acids can occur in D-form, L-form or in racematic form, preferably in the form that is dominant for them by nature.
Examples for these aldonic acids of the formula X include hexonic acid, allonic acid, altronic acid, galactonic acid, gluconic acid, gulonic acid, idonic acid, mannonic acid and talonic acid, preferably galactonic acid, gluconic acid, gulonic acid and mannonic acid. Further examples are derivatives of these hexonic acids, which are bonded glycosidically to the oxygen atoms in the 3, 4 or 6 position with a radical of formulas II through VII. The bonding can be α or β-glycosodic. The radicals II through V are galactopyranosyl and mannopyranosyl radicals. The radicals VI and VII are glucopyranosyl radicals (for the case where m = 0) and α (1->4) or β (1->4) chained oligoglucopyranosyl radicals (if m = 1 through 6). In the formulas VI and VII, the index m preferably represents 0 or 1. The saccharide units that are chained with the aldonic acid are generally available in D-form. Example for hexonic acids of the general formula X that are substituted with radicals of the formulas II through VII are

glucopyranosyl gluconic acids, glucopyranosyl mannonic acids, glucopyranosyl galactonic acids, galactopyranosyl gluconic acids, mannopyranosyl gluconic acids, mannopyranosyl mannonic acids and oligoglucopyranosyl gluconic acids. Preferred are lactobionic acid (4-O-β-D-6-O-α-D-galactopyranosyl gluconic acid), mannobionic acid, cellobionic acid (4-O-β-D-glucopyranosyl gluconic acid) and maltobionic acid (4-O-α-D-glucopyranosyl gluconic acid) as well as maltotrionic acid and cellotrionic acid.

Examples for inorganic and organic salts are ammonium, lithium, sodium, potassium, magnesium, calcium, aluminum salts and salts with ethanolamine, triethanolamine, morpholine, pyridine and piperidine. Preferred are sodium, potassium, calcium, aluminum and ethanolamine salts.

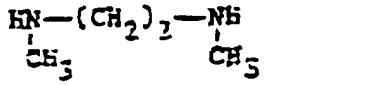
Examples for the straight chain or branched chain saturated alkylene radicals with 2 to up to 22 carbon atoms representing group A are ethylene-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, deca-, undeca-, dodeca-, tetradeca-, hexadeca-, octadeca-, icosa- and docosamethylene as well as methylethylene, methylpropylene, methylbutylene, methylpantylene and dimethylethylene. Preferred are ethylene-, tri-, tetra-, hexa-, nona-, dodeca- and docosamethylene as well as methylethylene and methylpantylene.

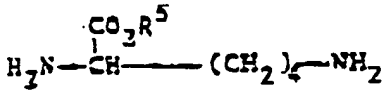
Examples for arylene radicals with which the alkylene radical of group A can be interrupted are phenylene, naphthylene, anthrylene, phenantrhylene and fluorenylene. Preferred are ortho-, meta- and para-phenylene radicals.

Examples for cycloalkylene radicals with which the alkylene radical of Group A can be interrupted are cyclopantylene, cyclohexylene, cycloheptylene and cyclooctylene, with 1,3 and 1,4-cyclohexylene being preferred.

In a preferred version, the straight chain or branched chain, saturated alkylene radical of Group A has 2 to 12 carbon atoms. If the straight chain or branched chain, saturated alkylene radical of Group A is interrupted with one of the above-mentioned radicals or groups, it should preferably be 1 or 2 of such radicals or groups.

Specific examples for the alkylene radicals representing group A in accordance with the definition are the groups that can be deduced from the following α,-diamines:

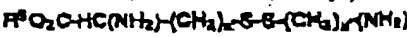




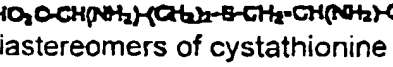
Enantiomers of lysine (R^6 = H) and its esters (R^5 = C_1-C_6-alkyl)

<u>with S-atoms:</u>

diastereomers of lanthionine (R^5 = H)
and ester (R^5 = C_1-C_6-alkyl)



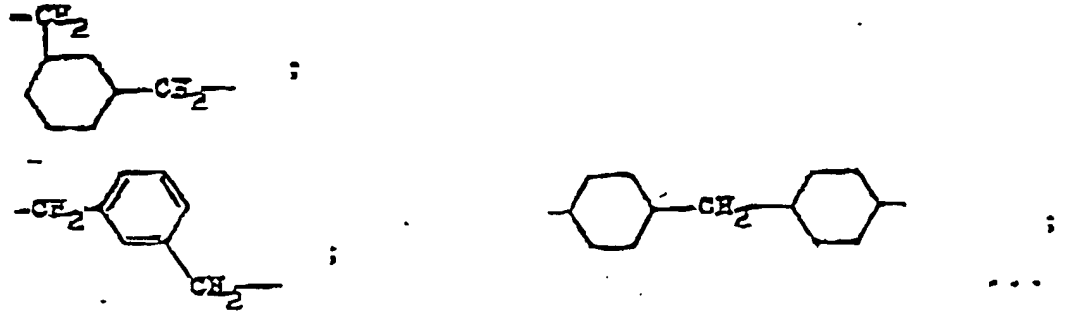
diastereomers of cystine (x = 1, R^5 = H)
and ester (R^5 = C_1-C_6-alkyl)
diastereomers of homocystine (x = 2, R^5 = H)
and ester (R^5 = C_1-C_6-alkyl)

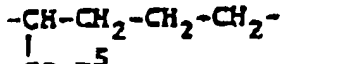


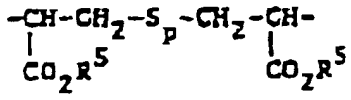
diastereomers of cystathionine

With NH Groups:	
$H_2N(-CH_2-CH_2-NH)_x-CH_2-CH_2-NH_2$	x = 1 diethylenetriamine x = 2 triethylenetetramine x = 3 tetraethylenepentamine
$H_2N-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_3-NH_2$	1,9-diamino-3,7-diazanonan
$H_2N-(CH_2)_3-NH-(CH_2)_2-NH-(CH_2)_3-NH_2$	1,10-diamino-4,7-diazanonan
$H_2N-(CH_2)_6-NH-(CH_2)_6-NH_2$	bis-(6-aminohexyl)amine
$H_2N-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_4-NH_2$	spermine
$H_2N-(CH_2)_4-NH-(CH_2)_3-NH_2$	spermidine
$H_2N-(CH_2)_3-NH-(CH_2)_3-NH-(CH_2)_6-NH_2$	1,11-diamino-4,8-diazaundecane
With O-atoms:	
$H_2N-(CH_2)_2-O-(CH_2)_2-NH_2$	Bis-(2-aminoethyl)ether

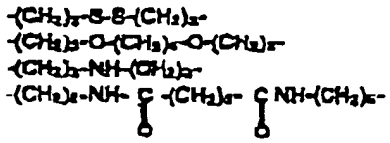
Preferably, group A can stand for the following radicals:





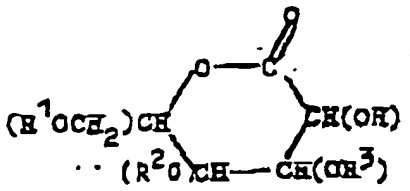


with p = 1 or 2

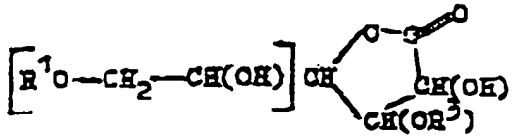


Examples for C_1-C_6-alkyl radicals of the groups R^4, R^5 and R^6 are methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, tert. Butyl, neopentyl, with methyl, ethyl, n-propyl, isopropyl, tert. Butyl and n-butyl being preferred.

The invention also concerns a method for preparing the amides of bis-aldonic acid of the general formula I. For this, analogue to familiar methods from literature (see above-mentioned literature list), the lactones of the aldonic acid X are reacted in a solvent with a diamino compound of the general formula R^4-HN-A-NHR^4, wherein R^4 has the meaning as specified above. For this, the lactones used can have the 1,5-lactone form of the general formula VII or also the 1,4 lactone form of the general formula IX.



(VIII)



(IX)

They can be obtained by splitting off water from the aldonic acids X. The aldonic acids can be obtained in methods we know from literature (e.g. W. N. Emmerling, S. Pfannemüller, Starch 33 (6), 202 (1981); R. Schaffer, H. S. Isbell, J. Am. Chem. Soc. 81, 2178 (1959), H. W. Diehl et al., Carbohydrate Research 38, 384 (1974))

through electrochemical or hypohalogenide oxidation from the corresponding aldoses.
For the preparation of the amides of bis-aldonic acids at issue, 2 mols aldonic acid lactone are used per mol diamino compound.
Suitable solvents for the reaction are methanol, ethanol, ethyleneglycol, dimethylsulfoxide, dimethylformamide or N-methylpyrrolidone. Preferred are dimethylformamide.
The reaction times are several hours up to several days, preferably between 5 and 8 hours.
The reaction temperatures are between room temperature and the temperature of ebullition of the respective solvent, preferably between 40 and 80°C (104 and 176°F).
The amides of bis-aldonic acid crystallize either from the reaction solution or can be precipitated by adding an organic solvent. Suitable substances are methanol, ethanol, isopropanol or acetone, preferably isopropanol.
In a preferred version of the invented method, the compounds of formula I are obtained from the aldonic acids of formula X without isolation of the lactones.
From - commercially available or those synthesized in accordance with methods known from literature (see above) - alkali or alkaline earth salts of the aldonic acids X an aqueous solution of the free aldonic acid X is prepared through cation exchange and then concentrated down. The lactones that correspond to the aldonic acids X are now created by splitting off water without isolation. For this purpose, the residue is dissolved in a high-boiling solvent, which leads to an aldonic acid and lactone mixture containing water. Examples of high-boiling solvents are dimethylsulfoxide, dimethylformamide, N-methylpyrrolidone, dimethoxymethylether etc.; preferred is dimethylformamide. Now a second, low-boiling solvent is added, which can form an azeotrope with water. Suitable solvents are e.g. n-pentane, n-hexane, cyclohexane, benzene etc.; preferred is n-hexane. On the water separator, water is now split off quantitatively from the aldonic acids. Then the low-boiling solvent is distilled off and the lactone, which can be found in the remaining, high-boiling solvent, is reacted with the diamino compound with isolation. The reaction temperatures are between 20 and 120°C (68 - 248°F), preferably between 50 and 80°C (122 and 176°F). The reaction products are obtained by precipitating them with an organic solvent. Suitable solvents are e.g. diethyl and other ethers, methanol, ethanol, isopropanol, carboxylic acid ester and acetone. Preferred are isopropanol and acetone. If necessary, the compounds can be released by treating them with acid and base ion exchanges of unreacted original compounds.

Further processing of the amides of bis-aldonic acid at issue into polysulphated products as well as those products themselves including their pharmacological properties are described in the German patent application P..... with the same applicant from the same application day (Case PSE-BAA, Title: "Polysulphuric Acid from Amides of Bis-Aldonic Acids and Their Derivatives, Method for their Preparation and Medications"), whose disclosure will be included here by referencing it.
The following examples explain the preparation of the compounds at issue as well as their further processing.

Example 1

N,N'-1,3-Propanediylbis-D-Gluconamide

Dissolve 7.13 g D(+)-gluconic acid-1,5-lactone in 40 ml amine-free dimethylformamide and mix it with 1.67 ml 1,3-diaminopropane. Warm to 60°C (140°F) and stir for 5 hours. The precipitation that is obtained is filtered off, rinsed with methanol and dried. This results in 7.96 g of a white powder.

Melting Point:	165-173°C (329-343°F)
IR (KBr):	ν = 3540, 2880, 2815, 2880, 1650, 1537, 1100, 1040 cm^{-1}
^{1}H-NMR (D_2O):	δ 1.78 (dt,2H, 6,5Hz); 3,30 (t, 4H, 6,5Hz); 3.4 - 4,0 (m, 8H); 4,09 (m, 2H); 4,30 (d, 2H, 3Hz); 4,70 (H_2O, LSt.)

Example 2

N,N'-1,12-Dodecanediylbis-D-Gluconamide

Suspend 7.1 g D-gluconic acid-1,5-lactone in 90 ml amine-free dimethylformamide, mix it with 4.0 g diaminododecane and stir the mixture for 5 hours at 60°C (140°F). When the mixture has cooled down, stir in 0.3 l methanol, collect the solid matter and rinse with methanol. Now suspend the solid matter in 1 N HCl, stir for one hour at room temperature, collect the solid matter again and rinse it with water, acetone and finally with diethylether. This results in 9.9 g of a white powder.

Melting Point:	192-195°C (377-383°F)
IR (KBr):	ν = 2920, 2850, 1630, 1550, 1085, 1027 cm^{-1}
^{1}H-NMR (DMSO - d_6):	δ 0,7 - 1,8 (m, 20H); 3,06 (m, 4H); 3,25 - 3,75 (m, 8H); 3,75 - 4,2 (m, 4H); 4,40 (S, 10H); 7,51 (t, 2H, 5,5Hz); i. St.: Tetramethylsilan

Example 3

N,N'-1,3-Propanediylbis [4-O-β-D-Galactopyranosyl-D-Gluconamide]

Dissolve 385. 4 g calcium lactobionate in 1.2 l water and treat the solution for 1 hour with 0.7 l Lewatit S 100 (H^+ form) with the batch procedure. Vacuum off and rinse the exchange with 2 x 1 l water. The united eluates are then further reduced in vacuum. Now dissolve the glass-like residue in 800 ml amine-free dimethylformamide, add 800 ml n-hexane and heat on the water separator while stirring vigorously until it boils. After the process of splitting of water has been completed, distill of the n-hexane, mix it with 43 ml 1,3-diaminopropane and stir for 7 hours at 63°C (145°F). Now stir the mixture into 5 l isopropanol, collect the solid matter and rinse with 1 l isopropanol. Upon drying, 350 g of a white solid matter is obtained. For the cleaning process, dissolve it in 2 l water. The solution is treated for 1 hour with 100 ml Lewatit S 100 (H^+ form), then with 100 ml Amberlyst A 21 (OH – form). Upon lyophilization, you obtain the compound described in the title in pure form.

Melting Point:	125-132°C (257-269°F)
IR (KBr):	ν = 2930, 1645, 1550, 1080 cm⁻¹
^{1}H-NMR (D_2O):	δ 1,76 (dt, 2H, 8Hz); 3,27 (t, 4H, 8Hz); 3,4 - 4,1 (m, 20H); 4,15 (t, 2H, 3Hz); 4,39 (d, 2H, 3Hz); 4,54 (d, 2H, 7Hz); 4,70 (H_2O, i.St.)
^{13}C-NMR (D_2O):	δ 30,79; 38,99; 63,73; 64,86; 71,30; 73,12; 73,74; 74,14; 74,50; 75,06; 75,18; 77,92; 83,71; 106,10; 176,84 i. St.: CH_3OH δ 51,58

Example 4

N,N'-1,6-Hexanediylbis[4-O-β-D-Galactopyranosyl-D-Gluconamide]

Suspend 17.0 g lactobionic acid-1,5-lactone in 100 ml amine-free dimethylformamide, mix it with 2.9 g diaminohexane and stir for 6 hours at 80°C (176°F). Once it has cooled off, it is filtered and the filtrate is stirred into 1 l diethylether. The in part oily precipitation is dissolved in 50 ml water and treated with 80 ml ion exchange (Merck 4765, H^+ form). The mixture is filtered, and upon lyophilization 19.5 g of a colorless powder is obtained, that decomposes beyond 175°C (347°F) while turning brown.

IR:	ν = 2930, 2880, 1645, 1548, 1080 cm⁻¹
^{1}H-NMR (D_2O):	δ 1,0 - 1,8 (m, 8H); 3,25 (t, 4H, 5,5Hz); 3,3 - 4,1 (m, 20H); 4,15 (t, 2H, 8Hz); 4,38 (d, 2H, 3Hz); 4,55 (d, 2H, 7Hz); 4,70 (H_2O) i. St.: 3-Trimethylsilyl-propansulfonsäure-Na-Salz
^{13}C-NMR (D_2O):	δ 28,19; 30,89; 41,83; 63,82; 64,84; 71,28; 73,08; 73,72; 74,12; 74,85; 75,16; 77,97; 83,51; 106,08; 176,48 i. St.: CH_3OH δ 51,54

Example 5

N,N'-1.12-Dodecanediylbis[4-O-β-D-Galactopyranosyl-D-Gluconamide]

Suspend 40.8 g lactobionic acid-1,5-lactone in 150 ml amine-free dimethylformamide, mix it with 12.0 g 1,12-diaminododecane and stir the mixture for 6 hours at 60°C (140°F). While stirring, drop the mixture into 1.5 l isopropanol, The precipitation is rinsed with isopropanol and dissolved in 250 ml water. The mixture is first treated with 20 ml of an acid ion exchange (Lewatit S 100), then with a base ion exchange (Merck 4767). Upon lyophilization, 35.0 of a colorless powder is obtained.
Melting Point: 79-81°C (174-177°F)

IR:	ν = 2920, 2850, 1645, 1550, 1080 cm⁻¹
^{1}H-NMR (D_2O):	δ 0,9 - 1,8 (m, 20H); 3,24 (t, 4H; 6,5Hz); 3,4 - 4,1 (m, 20H); 4,17 (t, 2H, 3Hz); 4,38 (d, 2H, 3Hz); 4,55 (d, 2H, 7Hz); 4,88 (H_2O, i. St.)
^{13}C-NMR (D_2O):	δ 29,02; 31,58; 31,70; 41,86; 63,64; 64,66; 71,20; 73,06; 73,72; 74,17; 78,03; 78,20; 77,97; 83,72; 106,12; 176,24; i. St. CH_3OH 51,58

Example 6

N,N'-1,9-Nonanediylbis[4-O-β-D-Galactopyranosyl-D-Gluconamide]

Preparation and rinsing process as described in example 5. You obtain 15.0 of the compound described in the title from 15.0 g lactobionic acid-1,5-lactone and 3.47 g 1,5-diaminononane.

IR:	ν = 2930, 2860, 1650, 1545, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,9 - 1,9 (m, 14H); 3,20 (t, 4H, 5,5Hz); 3,3 - 4,1 (m, 20H); 4,15 (t, 2H, 3Hz); 4,39 (d, 2H, 3Hz); 4,55 (d, 7Hz); 4,88 (H_2O, LSt.)

Example 7

N,N'-1,12-Dodecanediylbis[4-O-β-D-Glucopyranosyl-D-Gluconamide]

Mix 2.04 g cellobionic acid-1,5-lactone (H.W. Diehl et al, Carbohydr. Res. 38, 384 (1974)) analog to example 5 with 0.60 g 1,12-diaminododecane and you obtain 0.60 g of the compound described in the title.

IR:	ν = 2925, 2850, 1645, 1545, 1075, 1040 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,7 - 1,9 (m, 20H); 3,0 - 4,6 (m, 30H); 4,68 (H_2O L St.)

Example 8

N,N'-1,12-Dodecanediylbis[4-O-α-D-Glucopyranosyl-D-Gluconamide]

Mix 20.0 g calcium-maltobionate (W.N. Emmerling, B. Pfannemüller, Starch 33, 202 (1961)) analog to example 3 with 1,12-diaminododecane and you will obtain 17.8 g of the product.

IR:	ν = 2925, 2850, 1650, 1545, 1145, 1075, 1030 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,7 - 1,9 (m, 20H); 3,20 (t, 4H, 5,5Hz); 3,3 - 4,4 (m, 24H); 5,15 (d, 2H, 3Hz); 4,88 (H_2O, LSt.)

Example 9

N,N'-1,12-Dodecanediylbis[6-O-α-D-Galactopyranosyl-D-Gluconamide]

Mix 3.96 g of potassium-maltobionate (Sigma-Chemie) analog to example 3 with 1.00 g 1,12-diaminododecane and you will obtain 3.3 g of the compound described in the title.

Melting Point:	114-123°C (237-253°F)
IR (KBr):	ν = 2925, 1655, 1648, 1550, 1150, 1080, 1030, 880 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,8 - 1,8 (m, 20H); 3,20 (m, 4H); 3,4 - 4,2 (m, 22H), 4,28 (d, 2H, 3Hz); 4,85 (s, 2H); 4,68 (H_2O, l. St.)

Example 10

N,N'-1,3-Propanediylbis [6-O-α-D-Galactopyranosyl-D-Gluconamide]

Preparation analog example 9. You obtain 3.0 g of the product from 3.96 g potassium-maltobionate and 0.35 g 1,3-diaminopropane.

Melting Point:	90-96°C (194-204°F)
IR (KBr):	ν = 2925, 1645, 1550, 1152, 1080, 1030, 875 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,78 (dt, 2H, 6,5 Hz); 3,30 (t, 4H, 6,5Hz); 3,4 - 4,2 (m, 22H); 4,33 (d, 2H, 3Hz); 4,96 (s, 2H); 4,70 (H_2O, l. St.)
^{13}C-NMR (D_2O):	δ 30,73; 38,96; 63,75; 70,94; 74,13; 71,90; 72,12; 73,06; 73,52; 74,52; 75,97; 100,99; 178,91

Example 11

N,N'-α,α'-m-Xylenediylbis[4-O-β-D-Galactopyranosyl-D-Gluconamide]

When using 17.0 g lactobionic acid-1,5-lactone and 3.3 ml 3-(aminoethyl)-benzylamine in a procedure in accordance with example 5, then 12.2 g of the title compound is obtained as a colorless powder.

IR:	ν = 2920, 1665, 1545, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 3,3 - 4,5 (m, 30H); 4,68 (H_2O); 7,24 (m, 4H)

Example 12

N,N'-4,4'-Dicyclohexylmethanediylbis[4-O-β-D-Galactopyranosyl-D-Gluconamide]

Preparation and rinsing process analog example 5 with 17.0 g lactobionic acid-1,5-lactone and 5.3 g 4,4'-diamino-dicyclohexylmethan. Yield: 21.3 g.

IR:	ν = 2930, 2850, 1645, 1545, 1080 cm^{-1}
^{1}H-NMR (D_2O):	δ 0,8 - 2,2 (m, 20H); 3,2 - 4,8 (m, 28H), 4,68 (H_2O)

Example 13

N,N'-1,6-(3,4-Dithiahexanediylbis)4-O-β-D-Galactopyranosyl-D-Gluconamide

Mix 17.0 g lactobionic acid-1,5-lactone and 5.83 g cystamine dihydrochloride in 50 ml amine-free DMG at room temperature with 6.9 ml triethylamine and then stir for 6 hours at 60°C (140°F). Precipitate with 500 ml ethanol and treat the precipitation as described in example 5. You will obtain 13.2 g of a white powder.

IR: ^{1}H-NMR (D_2O):	ν = 2925, 1650, 1545, 1080 cm^{-1} δ 2,90 (t, 4H, 6Hz); 3,2 - 4,1 (m, 24H); 4,18 (t, 2H, 3Hz); 4,38 (d, 2H, 3Hz); 4,55 (d, 2H, 7 Hz); 4,68 (H_2O, L St.)

Example 14

N,N'-1,7-(4-Azaheptanediylbis)4-O-β-D-Galactopyranosyl-D-Gluconamide

Suspend 17.0 g lactobionic acid-1,5-lactone in 100 ml amine-free dimethylformamide, mix it at room temperature with 2.28 ml bis-(3-aminopropyl)-amine and stir for 10 hours. Then stir for 4 hours at 40°C (104°F) and filter. The filtrate is then stirred into 900 ml acetone and upon the rinsing process with acetone and the drying process, 23.0 of white crystals is obtained. They are dissolved in 80 ml water and precipitated with 90 ml acetone. The in part oily precipitation is dissolved in 150 ml water, filtered and lyophilized. Yield: 16.5 g.

IR: ^{1}H-NMR (D_2O):	ν = 2920, 1650, 1545, 1080 cm^{-1} δ 1,82 (dt, 4H, 6Hz); 2,91 (t, 4H, 6Hz); 3,30 (t, 4H, 6Hz); 3,45 - 4,8 (m, 28H); 4,68 (H_2O)

Example 15

N,N'-1,12-(4,9-Dioxadodecanediylbis)4-O-β-D-Galactopyranosyl-D-Gluconamide

Preparation and rinsing process analog example 5. From 17.0 lactobionic acid-1,5-lacone and 5.1 g 1,12-diamino-4,9-dioxa-dodecane you will obtain 18.9 g of the title compound

^{1}H-NMR:	δ 1,4 - 2,0 (m, 8H); 3,1 - 4,1 (m, 32H); 4,5 (t, 2H, 3Hz); 4,38 (d, 2H, 3Hz); 4,55 (d, 2H, 7Hz)

Example 16

N,N'-Dimethyl-N,N'-1,2-Ethandiylbis(4-O-β-D-Galactopyranosyl-D-Gluconamide)

Preparation and rinsing process analog example 5. From 3.40 lactobionic acid-1,5-lacone and 0.44 g N,N'-dimethylethylenediamine you will obtain 3.0 g of the title compound

Melting Point:	125-133°C (257-271°F)
IR (KBr):	ν = 2930, 1640, 1400, 1075 cm^{-1}
^{1}H-NMR (D_2O):	δ 2,99, 3,16 (2s, 6H); 3,3 - 4,3 (m, 28H); 4,49 (d, 2H, 7Hz); 4,68 (H_2O, l. St.)

Example 17

N,N'-1,5-(1-Ethoxycarbonyl)-Pentanediylbis(4-O-β-D-Galactopyranosyl-D-Gluconamide)

Suspend 2.47 g lysineethylester-dihydrochloride in 40 ml amine-free dimethylformamide, mix it with

3.0 ml triethylamine and stir for 15 minutes. Then add 6.8 g lactobionic acid-1,5-lactone, warm to 60°C (140°F) and stir for 1 day. Filter and stir the filtrate into 400 ml isopropanol. The precipitation is collected, dissolved in 60 ml dimethylformamide and precipitated again with 300 ml isopropanol. The precipitation process is repeated, it is rinsed with isopropanol and diethylether and 4.05 g of a white powder is obtained.

Melting Point:	106°C (222°F)
IR:	ν = 2930, 1735, 1655, 1550, 1075 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,25 (t, 3H, 7Hz); 1,2 - 2,2 (m, 6H); 3,25 (t, 2H, 5,5Hz); 3,4 -4,6 (m, 28H); 4,68 (H_2O, l. St.)

Example 18

Decasodium N,N'-1,3-Propanediylbis(2,3,4,5,6-Penta-O-Sulfo-D-Gluconamide)

4.30 g N,N'-1,3-propanediylbis-D-gluconamide is suspended in 50 ml dried dimethylformamide, warmed to 40°C (104°F) and mixed while stirring with 23.9 pyridine-sulphurtrioxide complex. Upon just a few minutes, the product precipitates in form of the pyridinium salt as oil. After 1 hour, allow to cool off and decant off the remaining solution. The oil is dissolved in 50 ml water and brought to a pH of 10 with 5 N soda lye. The solution is filled up with water to 90 ml and stirred into 350 ml of a 1% sodium acetate solution. The precipitation is rinsed with methanol and dried. You obtain 18.6 g of a colorless powder. This is dissolved in 186 ml water. Then 227 ml methanol is stirred into the solution and it is allowed to stand for 15 hours. It is decanted off the precipitated oil and rubbed with methanol. Repeat the precipitation process until the compound described in the title is available in pure form.
Decomposes beyond 190°C (374°F).

IR (KBr):	ν = 2880, 1670, 1535, 1250, 1073, 1045, 1019, 770 cm^{-1}		
^{1}H-NMR (D_2O):	δ 1,87 (pt, 2H, 7Hz); 3,38 (dt, 4H, 7Hz); 3,9 -4,6 (m, 4H); 4,8 - 5,4 (m, 8H); 4,58 (H_2O, L St.)		
$[\alpha]_D^{20}$ = +28,2 (c = 5 in H_2O)			
Ultimate Organic Analysis:			
	ber.:	N 22,10 %	S 1,93 %
	gef.:	N 22,28 %	S 1,83 %
	^{13}C-NMR (D_2O):	δ 29,87; 38,85; 69,08; 77,58; 78,10; 78,38; 78,85; 171,33; l, St.: CH_3OH δ 51,56	

Example 19

Decasodium N,N'-1,12-Dodecanediylbis(2,3,4,5,6-Penta-O-Sulfo-D-Gluconamide)

Mix 5.60 g N,N'-1,12-dodecanediylbis-D-gluconamide analog example 18 with 25.5 g pyridine-sulphurtrioxide complex and you will obtain 20.5 of raw product. The pure product is obtained through gel chromatography of an aqueous solution in a Sephadex G-25 column. Upon lyophilization, a colorless powder is obtained, which decomposes between 175 and 189°C (347-372°F) while turning brown.

IR (KBr):	ν = 2930, 2858, 1665, 1555, 1250, 1072, 1042, 1010 cm^{-1}
^{1}H-NMR (D_2O):	δ 1,0 - 1,9 (m, 28H); 3,32 (m, 4H); 4,2 - 4,8 (m, 4H); 4,9 - 5,3 (m, 8H); 4,68 (H_2O, i.St.)
^{13}C-NMR (D_2O):	28,72; 30,52; 31,02; 42,50; 69,22; 77,87; 78,14; 78,66; 79,81; 171,09; i. St. CH_3OH 51,58

Example 20

Hexadecasodium N,N'-1,3-propanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

79.1 g of calcium lactobionate are dissolved in 240 ml of water and the solution is treated with 240 ml of Lewatit S 100 (H^+ form). The ion exchanger is washed using 3 x 200 ml of water and the combined solutions are concentrated as far as possible. The glass-like residue is dissolved in 700 ml of amine-free dimethylformamide and heated to boiling with 600 ml of n-hexane in a water separator. After water separation is complete, the n-hexane is evaporated off and 7.7 g of 1,3-diamino-propane in 50 ml of dimethylformamide are added to the solution at room temperature. After stirring for 5 hours at 60°C, the mixture is allowed to cool to about 30°C and is diluted with 450 ml of dimethylformamide, and 400 g of pyridine-sulfur trioxide complex are added rapidly portionwise under stirring. The mixture is stirred for 1 hour between 40° and 45°C and is allowed to cool. The supernatant is decanted from the deposited oil, and this is dissolved in 500 ml of water, and the solution is adjusted to pH = 10 using 30% strength sodium hydroxide solution. The solution is made up with water to a volume of 1.5 liters and stirred into 4.5 liters of a 1% methanolic sodium acetate solution. The precipitate is stirred with 1 liter of methanol, filtered off with suction, and dried. 250 g of yellowish powder are obtained. This is dissolved in 2 liters of water, 250 ml of 30% hydrogen peroxide are added, and the mixture is stirred for 1 hour at 45°C. After cooling, it is neutralized and made up to 2.5 liters with water. The solution is stirred into 3.06 liters of methanol and is allowed to stay for 15 hours. The supernatant is decanted from deposited oil, and the latter is triturated with methanol. After drying, 188.5 g of colorless powder are obtained. The precipitation procedure is repeated four times, and about 50 g of pure end compound are finally obtained as colorless powder which turns brown from 172°C with decomposition and does not melt under 250°C.

IR(KBr):	ν=2965,1665, 1552, 1250, 1055,1020, 927, 820cm^{-1}	
^{1}H-NMR (D_2O):	δ 1.82 (t, 2H, 6.5 Hz); 3.35 (t, 4H, 6.5 Hz); 3.9-4.4 (m, 8H); 4.4-4.8 (m, + H_2O-signal at 4.68 as i. std.); 4.8-5.4 (m, 10H)	
^{13}C-NMR (D_2O):	δ 30.31; 39.77; 68.36; 68.92; 74.22; 77.49; 77.79; 78.39; 78.76; 80.15; 103.55; 171.76; i. std.: CH_3OH δ 51.56	
$[\alpha]^D_{20}$ = +13.3° (c = 5 in H_2O)		
Elemental analysis		
calc.:	N: 1.17%	S: 21.49%
found:	N: 1.16%	S: 21.61%

Example 21

Pentadecasodium pentadeca-O-sulfo-N,N'-1,3-propanediylbis(4-O-β-D-galactopyranosyl-D-gluconamide)

3.77 g of N,N'-1,3-propanediylbis (4-O-β-D-galactopyranosyl-D-gluconamide) are dissolved in 60 ml of dry dimethylformamide and 13.5 g of pyridine-sulfur trioxide complex are added in portions at 40°C under stirring. After 1 hour, the mixture is worked up as in Example 18 and 10.3 g of yellowish, sulfate-containing crude product are obtained. This is dissolved in 90 ml of water, 10 ml of 30% hydrogen peroxide are added, and the mixture is stirred for 1 hour at 45°C. After cooling, 230 ml of methanol are stirred in, and the mixture is allowed to stay for 15 hours. The supernatant is decanted off from the deposited oil, the latter is triturated using methanol, and 6.72 g of sulfate-free product (having a sulfur content of 20.6%) are obtained. This is dissolved in 67 ml of water, 82 ml of methanol are stirred in, and the mixture is allowed to stay for 15 hours. The supernatant is decanted from the deposited oil, and a further 74 ml of methanol are stirred in. After 15 hours, the oil is isolated, and the fractional crystallization is repeated with it several times as above until the end compound is pure. 0.53 g of colorless powder, which decomposes from 180°C with brown coloration, is obtained.

IR (KBr):	ν = 2960, 1660, 1550, 1250, 1055, 1020, 930, 820 cm^{-1}		
^{1}H-NMR (D_2O):	δ 1.87 (t, 2H, 6 Hz); 3.42 (t, 4H, 6 Hz); 3.9-4.5 (m, 8H); 4.5-4.85 (m+ H_2O signal at 4.68 as i. std.); 4.85 - 5.3 (m, 10H)		
^{13}C-NMR (D_2O):	δ 30.53; 39.79; 68.46; 69.11; 72.28; 74.36; 74.56; 77,43; 77.88; 78.14; 78.49; 79.03; 79.61; 79.84; 80.43; 103.45; 171.82; 172.61; i. std.: CH30Hδ51.56		
Elemental analysis:	calc.:	N 1.23%	S 21.04%
	found:	N 1.21%	S 20.91%

Example 22

Hexadecamorpholinium N,N'-1,3-propanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

A solution of 1.76 g of the sodium salt from Example 20 is treated for 15 minutes with 16 ml of Lewatit S-100 (H^+-form), the ion exchanger is filtered off, and 1.03 g of morpholine are added to the filtrate. After lyophilization, 2.40 g of yellowish powder are obtained. Decomposition from 120°C and black coloration at 210°C.

IR (KBr):	ν = 2950, 2780, 1665, 1563, 1450, 1426, 1250, 1097, 1015, 925, 893, 868, 810 cm^{-1}
^{1}H-NMR (D_2O):	δ 1.82 (dt,2H; 6.5 Hz); 3.15 (m, 64H); 3.35 (m, 4H); 3.90 (m, 64H); 4.0-4.4 (m, 8H); 4.4-4.8 (m, +H_2O signal at 4.70 as i. std.); 4.8-5.4 (m, 10H)

Example 23

Hexadecasodium N,N'-1,6-hexanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4;6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

16.3 g of N,N'-1,6-hexanediylbis(4-O-β-D-galactopyranosyl-D-gluconamide) are reacted with 75.0 g of pyridine-sulfur trioxide complex similarly to Example 18. After the first precipitation, 56.9 g of yellowish powder are obtained which is purified as in Example 20. About 15 g of the pure title compound are finally obtained in the form of colorless powder which sinters from 120°C.

Decomposition from 170°C with brown coloration.

IR (KBr):	ν = 2930, 2860, 1655, 1550, 1250, 1055, 1020,928, 810cm^{-1}
^{1}H-NMR (D20):	δ 1.1-1.9 (m, 8H); 3.37 (m, 4H); 3.9-4.5 (m, 8H); 4.5-4.85 (m + H_2O signal at 4.68 as in. std.); 4.85-5.3 (m, 10H)
^{13}C-NMR (D_2O):	δ 28.42; 30.74; 42.17; 68.56; 69.01; 74.39; 77.20; 77.80; 78.37; 78.94; 80.47; 103.21; 171.27; i. std. CH_3OH δ 51.56
$[\alpha]^D_{20}$ = + 9.9 (c = 5 in H_2O)	

Example 24

Hexadecasodium N,N'-1,9-nonanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

Preparation and purification are similar to Example 23. 45.0 g of crude product are obtained from 15.0 g of N,N'-1,9-nonanediylbis (4-O-β-D-galactopyranosyl-D-gluconamide) and 63.0 g of pyridine-sulfur trioxide complex. After purification, 10.5 g of colorless powder are obtained.

Decomposition between 192°-210°C with brown coloration

IR (KBr):	v = 2935, 2860, 1665, 1555, 1250, 1057, 1020, 925, 815 cm^{-1}
^{1}H-NMR (D20):	δ 0.9-1.9 (m, 14H); 3.29 (t, 4H, 6.5 Hz); 3.8-4.45 (m, 8H); 4.45-4.8 (m + H_2O-signal at 4.68 as i. std.); 4.8-5.4 (m, 10H)
^{13}C-NMR (D_2O):	δ 28.77; 30.83; 31.09; 31.32; 42.19; 68.69; 68.99; 74.46; 77.12; 77.79; 78.33; 78.93; 80.51; 103.11; 121.21 int. std.: CH_3OH, δ 51.56

Example 25

Hexadecasodium N,N'-1,12-dodecanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

Preparation and purification are similar to Example 23. 13.30 g of crude product are obtained from 4.23 g of N,N'-1,12-dodecanediylbis (4-O-β-D-galac-topyranosyl-D-gluconamide) and 19.1 g of pyridine-sulfur trioxide complex. After purification, 3.5 g of pure end compound as colorless powder are obtained.

Decomposition between 188°- 198°C with brown coloration.

IR (KBr):	v = 2940, 2880, 1665, 1555, 1250, 1055, 1020,930,820 cm^{-1}
^{1}H-NMR (D20):	δ 0.9-1.9 (m, 20H); 3.35 (t, 4H, 6.5 Hz); 3.9-4.5 (m, 8H); 4.5-4.8 (m, + H_2O-signal at 4.70 as i. std.); 4.8-5.4 (m, 10H)
^{13}C-NMR (D_2O):	δ 28.74; 30.80; 31.09; 31.44; 42.18; 68.76; 68.96; 74.50; 77.08; 77.80; 78.29; 78.94; 80.51; 103.07; 171.19 i. std.: CH_3OH δ 51.56

Example 26

Hexadecasodium N,N'-1,12-dodecanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-glucopyranosyl)-D-gluconamide]

0.68 g of crude or 0.10 g of pure product are obtained from 0.34 g of N,N'-1,12-dodecanediylbis (4-O-β-D-glucopyranosyl-D-gluconamide) and 1.12 g of pyridine-sulfur trioxide complex similarly to Example 23. Decomposition from 148°C to 159°C. with brown coloration.

IR (KBr):	v = 2930, 2855, 1670, 1560, 1250, 1070, 995, 935,800 cm^{-1}
^{1}H-NMR (D20):	δ 0.8-1.8 (m, 20H); 3.30 (m, 4H); 3.7-4.8 (m + H_2O signal at 4.68 as i. std.); 4.8-5.3 (m, 10H)
^{13}C-NMR (D_2O):	δ 28.92; 30.95; 31.32; 31.64; 42.34;' 69.20; 70.12; 75.57; 77.44; 77.67; 77.85; 79.33; 79,41; 79.97; 81.08; 102.53; 171.27; i. std.: CH_3OH δ 51.56

Example 27

Hexadecasodium N,N'-1,12-dodecanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-α-D-glucopyranosyl)-D-gluconamide]

47.5 g of crude or 3.0 g of pure product are obtained from 12.8 g of N,N'-1,12-dodecanediylbis (4-O-α-D-glucopyranosyl-D-gluconamide) and 64.6 g of pyridine-sulfur trioxide complex similarly to Example 23. Decomposition from 175°C to 189°C with brown coloration.

IR (KBr):	v = 2930, 2860, 1660, 1560, 1250, 1000, 943, 805 cm^{-1}
^{1}H-NMR (D20):	δ 1.0 - 1.9 (m, 20H); 3.27 (m, 4H); 4,0-4.82 (m +signal for H_2O at 4.68 as i. std.); 4.82-5.25 (m, 10H); 5.52 (d, 2H, 3 Hz)
^{13}C-NMR (D_2O):	28.84; 30.69; 31,15; 31.47, 42.41; 68.51; 69.29; 71.95; 76.14; 76.82; 77.91; 78.30; 78.44; 79.98; 98.93; 171.27

Example 28

Hexadecasodium N,N'-1,12-dodecanediylbis[2.3.4,5-tetra-O-sulfo-6-O-(2,3,4,6-tetra-O-sulfo-α-D-galacto-pyranosyl)-D-gluconamide]

9.7 g of crude or 3.4 g of pure product, which sinters at 57°C, are obtained similarly to Example 23 from 3.30 g of N,N'-1,12-dodecanediylbis (6-O-α-D-galac-topyranosyl-D-gluconamide) and 14.9 g of pyridine-sulfur trioxide complex.

Decomposition from 182°C with brown coloration.

IR (KBr):	v = 2930, 2855, 1650, 1555, 1250, 1050, 1027,830cm^{-1}
^{1}H-NMR (D20):	δ 1.0-1.9 (m, 20H); 3.25 (m, 4H); 2.9-4.4 (m, 8H); 4.4-4.8 (m + H_2O-signal at 4.68 as i. std.); 4.8-5.25 (m, 10H); 5.38 (d, 2H, 3 Hz)
^{13}C-NMR (D_2O):	δ 28.72; 30.58; 31.03; 31.34; 42.30; 69.14; 69.77; 70.66; 74.51; 74.92; 77.91; 78.21; 78.49; 78.93; 80.75; 99.12; 171.26;.i. std.; CH_3OH δ 51.56

Example 29

Hexadecasodium N,N'-1,3-propanediylbis[2,3,4,5-tetra-O-sulfo-6-O-(2,3,4,6-tetra-O-sulfo-α-D-galactopyranosyl)-D-gluconamide]

0.96 g of crude or 0.50 g of pure product are obtained from 0.34 g of N,N'-1,3-propanediylbis (6-O-α-D-galac-topyranosyl-D-gluconamide) and 2.0 g of pyridine-sulfur trioxide complex similarly to Example 23. Decomposition from 168°C with brown coloration.

IR (KBr):	v = 1640, 1550, 1250,1050,1025, 830 cm^{-1}
^{1}H-NMR (D20):	δ 1.85 (t,2H, 6.5 Hz); 3.35 (t, 4H, 6.5 Hz); 3.9-4.4 (m, 8H); 4.4-4.8 (m + H_2O signal at 4.68 as i. std.); 4.8-5.25 (m, 10H); 5.36 (d, 2H, 3 Hz)
^{13}C-NMR (D_2O):	δ 30.13; 39.84; 69.17; 69.86; 70.74; 74.53; 74.97; 78.00; 78.17; 78.37; 79.00; 80.81; 99.18; 171.70; i. std; CH_3OH δ 51,57

Example 30

Hexadecasodium N,N'-α,α'-m-xylenediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

28.0 g of crude or 5.3 g of pure product are obtained from 12.0 g of N,N'-α,α'-m-xylenediylbis (4-O-β-D-galactopyranosyl-D-gluconamide) and 58.8 g of pyridine-sulfur trioxide complex similarly to Example 23. Decomposition from 157°C with brown coloration.

IR (KBr):	v = 2960, 1660,1550,1250,1055,1020,930, 815 cm^{-1}
^{1}H-NMR (D20):	δ 3.9-4.85 (m + H_2O-signal at 4.68 as i. std.), 4.85-5.4 (m, 10H); 7.38 (s, 4H)
^{13}C-NMR (D_2O):	δ 45.51; 68.63; 69.15; 74.42; 77.24; 77.67; 77.91; 78.49; 79.08; 80.70; 103.29; 128.15; 128.86; 131.64; 140.80; 171.88; i. std. CH_3OH δ 51.56

Example 31

Hexadecasodium N,N'-4,4'-dicylcohexylmethanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

70.7 g of crude or 15.2 g of pure product, which sinters from 120°C, are obtained similarly to Example 23 from 25.7 g of N,N'-4,4'-dicyclohexylme-thanediylbis (4-O-β-D-galactopyranosyl-D-gluconamide) and 114.7 g of pyridine-sulfur trioxide complex.

Decomposition from 180°C with brown coloration.

IR (KBr):	v = 2930, 2860, 1660, 1550, 1250, 1055, 1020, 928, 815 cm^{-1}
^{1}H-NMR (D20):	δ 0.6-2.4 (m, 20H); 3.65 (m, 2H); 3.9-4.5 (m, 8H); 4.5-4.85 (m + H_2O-signal at 4.68 as i. std.); 4.85-4,4 (m, 10H)
^{13}C-NMR (D_2O):	30.18; 30.36; 30.75; 34.09; 44.40; 46.20; 49.45; 52.33; 68.27; 68.75; 74.35; 77.80; 78.41; 78.68; 79.49; 104.09; 170.61; i. std. CH3OH δ 51,56
$[\alpha]^D_{20}$ = + 10.0 (c = 5 in H_2O)	

Example 32

Hexadecasodium N,N'-1,6-(3,4-dithiahexanediylbis)[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

38.0 g of crude and 8.5 g of pure product are obtained from 11.2 g of N,N'-1,6-(3,4-dithiahexanediylbis) 4-O-β-D-galactopyranosyl-D-gluconamide and 53.4 g of pyridine-sulfur trioxide complex similarly to Example 23.

Decomposition from 163°C with brown coloration.

IR (KBr):	v = 2965,1665, 1550, 1250, 1055, 1015, 930, 810 cm^{-1}
^{1}H-NMR (D20):	δ 2.96 (t, 4H, 6.5 Hz); 3.69 (m, 4H); 4.0-4.47 (m, 8H); 4.45-4.8 (m + H_2O-signal at 4.68 as i. std.); 4.8-5.3 (m, 10H)
^{13}C-NMR (D_2O):	δ 38.72; 41.06; 68.68; 69.05; 74.48; 77.40; 77.87; 78.46; 80.46; 103.48; 171.86; i. std. CH_3OH δ 51.56

Example 33

Hexadecasodium N,N'-1,7-(4-azaheptanediylbis)[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

15.4 g of crude and 2.2 g of pure product are obtained from 11.0 g of N,N'-1,7-(4-azaheptanediylbis) 4-O-β-D-galactopyranosyl-D-gluconamide and 50.0 g of pyridine-sulfur trioxide complex similarly to Example 23.

Decomposition from 165°C with brown coloration.

IR (KBr):	v = 2960, 2925, 2855, 1650, 1550, 1250, 1055, 1020,927,820 cm^{-1}
^{1}H-NMR (D20):	δ 2.98 (m, 2H); 3.17 (t, 4H, 7 Hz); 3.44 (t, 4H, 6 Hz); 3.9-4.4 (m, 8H); 4.4-4.85 (m + H_2O signal as i. std. at 4.68); 4.85-5.3 (m, 10H)
^{13}C-NMR (D_2O):	δ 28.11; 39.08; 48 12; 68.65; 69.24; 74.45; 76.94; 77.93; 78.46; 79.09; 80.71; 103.13; 172.06

Example 34

Hexadecasodium N,N'-1,12-(4,9-dioxadodecanediylbis)[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

37.1 g of crude and 9.3 g of pure product, which sinters from 120°C are obtained from 18.2 g of N,N'-1,12-(4,9-dioxadodecanediylbis) 4-O-β-D-galac-topyranosyl-D-gluconamide and 59.0 g of pyridine-sulfur trioxide complex according to Example 23.

Decomposition from 170°C with brown coloration.

IR (KBr):	v = 2960, 2880, 1665, 1555, 1250, 1055, 1022, 928, 815 cm^{-1}
^{1}H-NMR (D20):	δ 1.64 (m, 4H); 1.88 (t, 4H, 6.5 Hz); 3.0-3.9 (m, 12H); 3,9-4.45 (m, 8H); 4.45-4.8 (m + H_2O-signal at 4.68 as i. std.); 4.8-5.3 (m, 10H)
^{13}C-NMR (D_2O):	δ 27.82; 30.78, 39.02; 68.64; 69,01; 70.54; 72.96; 74.44; 77.02; 77.79; 78.33; 78.94; 80.52; 103.10; 171.45; i. std.: CH_3OH δ 51.56
$[\alpha]^D_{20}$ = + 9.0 (c = 5 in H_2O)	

Example 35

Hexadecasodium N,N'-dimethyl-N,N'-1,2-ethanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-gluconamide]

8.2 g of crude and 1.2 g of pure product are obtained from 2.50 g of N,N'-dimethyl-N,N'-1,2-ethanediylbis (4-O-β-D-galactopyranosyl-D-gluconamide) and 12.4 g of pyridine-sulfur trioxide complex similarly to Example 23.

Decomposition from 188°C to 200°C with brown coloration.

IR (KBr):	v = 2970, 1650, 1250, 1015, 930, 815 cm^{-1}
^{1}H-NMR (D20):	δ 3.0-4.0 (m with s at 3.35; 10H); 4.0-4.7 (m, 14H); 4.70 (H_2O, i. std.); 4.9-5.4 (m, 10H); 5,54 (d, 2H, 4 Hz)
^{13}C-NMR (D_2O):	δ 38.96; 48.28; 68.36; 69.25; 74.17; 75.11; 77.26; 77.73; 78.00; 78.45; 78.76; 79.80; 103.35; 171.25; i. std.: CH_3OH, δ 51.56

Example 36

Hexadecasodium N,N'-1,5-(1-ethoxycarbonyl)-pentanediylbis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galac-topyranosyl)-D-gluconamide]

8.7 g of crude and 1.2 g of pure product, which sinters from 60°C, are obtained from 3.6 g of N,N'-1,5-(1-ethoxycarbonyl)-pentanediylbis (4-O-β-D-galac-topyranosyl-D-gluconamide) and 15.8 g of pyridine-sulfur trioxide complex according to Example 23.

Decomposition from 161°C with brown coloration.

IR (KBr):	v = 1730, 1650, 1550, 1250, 1055,1020, 930, 810cm^{-1}
^{1}H-NMR (D20):	δ 1.0-2.2 (m, 9H, with t at 1.31, 7 Hz); 3.30 (m, 2H); 3.9-4.8 (m with H_2O-signal at 4.68 as i. std.); 4.8-5.3 (m, 10H)
^{13}C-NMR (D_2O):	δ 15.94; 29.68; 30.54; 33.17; 41.87; 55.93; 65.19; 68.23; 68.53; 69.04; 74.36; 77.33; 79.81; 78.45; 78.80; 79.61; 80.47; 103.36; 103.99; 171.39; 171.65; 176.12

Example 37

N,N'-1,3-Propanediylbis-D-gulonamide

3.56 g of D-gulono-γ-lactone and 0.84 ml of 1,3-diaminopropane are dissolved in 40 ml of dimethylformamide, and the mixture is stirred for 6 hours at 60°C.

The mixture is then stirred into 200 ml of isopropanol, and the precipitate is washed with isopropanol and diethyl ether. The solid is dissolved in 20 ml of imethylformamide and precipitated again with 200 ml of isopropanol. The precipitate is dissolved in water and freeze-dried. 2.2 g of colorless powder are obtained.

IR (KBr):	ν = 2930, 2890, 1645, 1545, 1440, 1080 cm^{-1}
^{1}H-NMR (D20):	δ 1.74 (dt,2H, 6.5 Hz); 3.27 (t, 4H, 6.5 Hz); 3.45 - 4.05 (m, 10H); 4.23 (d, 2H, 6 Hz); 4.68 (H_2O, i. std.)
^{13}C-NMR (D_2O):	δ 30.65; 39.02; 65.13; 72.64; 74.69; 75.00; 75.12; 176.78; i. std. CH_3OH δ 51.56

Example 38

N,N'-1,2-Propanediylbis-D-galactonamide

4.1 g of the end compound as colorless powder are obtained similarly to Example 37 from 7.12 g of D-galactono-γ-lactone and 1.48 g of 1,2-diaminopropane.

IR (KBr):	ν = 2940, 1656, 1552, 1109, 1055, 1044, 1028, 865 cm^{-1}
^{1}H-NMR (D20):	δ 1.18 (d, 3H, 6 Hz); 3.1-4.6 (m, 15H); 4.68 (H_2O, i. std.)
^{13}C-NMR (D_2O):	δ 19.64; 19.77, 46.16; 47.87; 48.10; 65.90; 71.93; 72.64; 73.49; 177.75; 178.42; 178.54

Example 39

N,N'-1,4-Butanediylbis-L-mannonamide

2.4 g of the end compound are obtained as colorless powder similarly to Example 18 from 3.56 g of L-mannono-γ-lactone and 0.90 g of potrescine.

Decomposition from 181°C to 188°C with brown coloration

IR (KBr):	v = 2955, 2925, 2855, 1643, 1555, 1231, 1098, 1043, 1031, 880, 740, 640 cm^{-1}
^{1}H-NMR (D20):	δ 1.58 (m, 4H); 3.30 (m, 4H); 3.75 (m, 8H); 4.02 (d, 2H, 7 Hz); 4.26 (d, 2H, 7 Hz); 4.68 (H_2O i. std.)
^{13}C-NMR (D_2O):	δ 28.42; 41.38; 65.67; 72.58; 72.76; 73.43; 75.19; 177.09

Example 40

N,N'-Dilactobionoylhydrazine

6.1 g of crude product are obtained similarly to Example 37 from 6.8 g of lactobiono-1,5-lactone and 0.5 ml of hydrazine hydrate. Column chromatography over Fractogel TSK HW 40S yields the pure product as colorless powder after freeze-drying.

Example 41

Decasodium N,N'-1,3-propanediylbis(2,3,4,5,6-penta-O-sulfo-D-gulonamide)

9.8 g of crude or 6.4 g of pure product as colorless powder are obtained similarly to Example 18 from 2.2 g of N,N'-1,3-propanediylbis-D-gulonamide and 12.3 g of pyridine-sulfur trioxide complex. Decomposition from 185°C with brown coloration.

IR (KBr):	v = 2960, 1675, 1555, 1250, 1070, 1010, 925, 805 cm^{-1}
^{1}H-NMR (D20):	δ 1.85 (m, 2H); 3.34 (m, 4H); 4.52 (d, 4H, 3.5 Hz); 5.07 (m, 6H); 5.34 (d, 2H, 3.5 Hz); 4.68 (H_2O, i. std.)
^{13}C-NMR (D_2O):	δ 30.05; 39.62; 68.78; 76.28; 76.41; 77.78; 80.14; 171.15; i. std. CH_3OH δ 51.55

Example 42

Decasodium N,N'-1,2-propanediylbis(2,3,4,5,6-penta-O-sulfo-D-galactonamide)

13.0 g of crude or 9.8 g of pure product as colorless powder are obtained similarly to Example 18 from 3.3 g of N,N'-1,2-propanediylbis-D-galactonamide and 19.5 g of pyridine-sulfur trioxide complex.

Decomposition from 191°C with brown coloration.

IR (KBr):	v = 2970, 1665, 1550, 1250, 1065, 1040, 1007, 900 cm^{-1}
^{1}H-NMR (D20):	δ 1.26 (d, 3H, 6.5 Hz); 2.9-4.3 (m, 3H); 4.3-4.6 (m, 4H); 4.68 (H_2O, i. std.); 4.8-5.3 (m, 8H)
^{13}C-NMR (D_2O):	δ 19.20; 45.94; 46.15; 47.61; 69.07; 78.42; 78.86; 79.90; 170.84; 171.03; 191.93 i. std. CH_3OH 8 51.57

Example 43

Decasodium N,N'-1,4-butanediylbis(2,3,4,5,6-penta-O-sulfo-L-mannonamide)

10.5 g of crude or 7.2 g of pure product as colorless powder are obtained similarly to Example 18 from 2.5 g of N,N'-1,4-butanediylbis-L-mannonamide and 14.1 g of pyridine-sulfur trioxide complex.

Decomposition from 180°C with brown coloration.

IR (KBr):	v = 2960, 2930, 2850, 1670, 1555, 1250, 1075, 1010,925 cm^{-1}
^{1}H-NMR (D20):	δ 1.65 (m 4H); 3.31 (m, 4H), 4.43 (m, 4H); 4.8-5.08 (m, 4H); 5.15 (m, 4H); 4.68 (H_2O, i. std.)
^{13}C-NMR (D_2O):	δ 27.98; 41.62; 69.15; 78.81; 79.36; 79.75; 170.93; i. std. CH_3OH 8 51.55

Example 44

Hexadecasodium N,N'-bis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)gluconoyl]-hydrazine

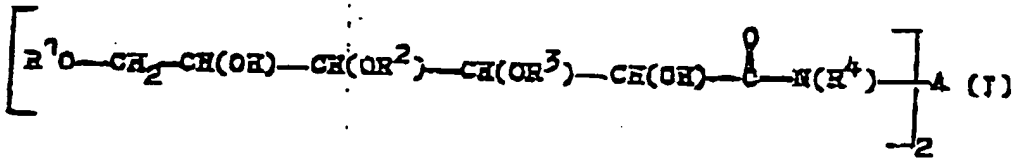
17.5 g of crude or 7.3 g of pure product are obtained similarly to Example 18 from 6.0 g of N,N'-dilacto-bionoylhydrazine and 33.7 g of pyridine-sulfur trioxide complex.

Example 45

5.000 kg of hexadecasodium N,N'-1,3-propanediyl-bis[2,3,5,6-tetra-O-sulfo-4-O-(2,3,4,6-tetra-O-sulfo-β-D-galactopyranosyl)-D-galactopyranosyl)-D-gluconamide] as dry substance are dissolved under stirring in 40 liters of water for injection. After adjusting the pH of the solution to 7.5 with a diluted sodium hydroxide solution, it is made up to 50.00 liters with water for injection and filtered through a membrane filter having a pore size of 0.2 µm. The solution is filtered off under aseptic conditions into ampoules of 1 ml and these are sealed off.

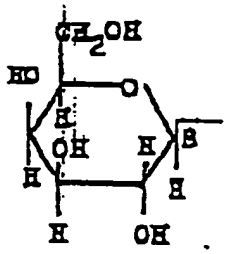
Claims

1. Bis-aldonamides of the general formula I

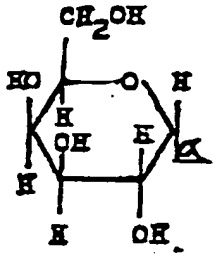


(I)

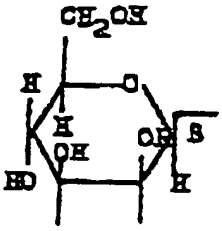
in which either all radicals R^1, R^2 and R^3 represent a hydrogen atom, or two of the radicals R^1, R^2 and R^3 represent a hydrogen atom and the third represents a radical of formulae II through VII



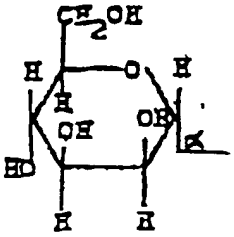
(II)



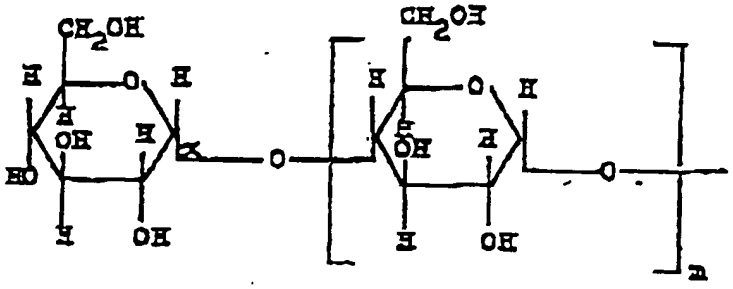
(III)



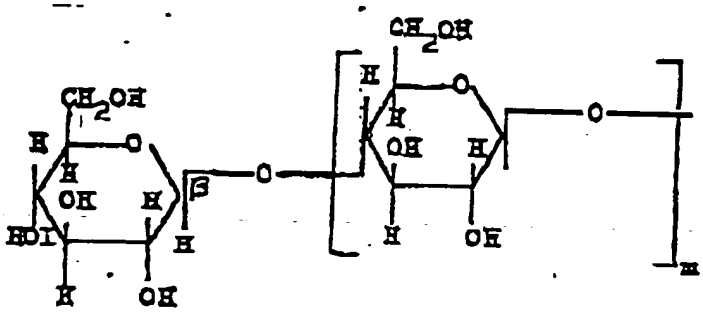
(IV)



(V)



(VI)

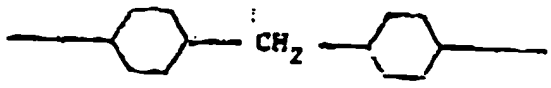


(VII)

wherein

m is 0, 1, 2, 3, 4, 5 or 6,

A in formula I represents a straight-chain or branched, saturated alkylene radical having 2 to 22 carbon atoms, and this alkyl radical is interrupted with up to 5 - O -, - S -, - S - S -, -S $(O)_n$, - C(=O)-NH- and/or - NR^6-groups or cycloalkylene or arylene radicals, or A is a simple bond or the radical



and n is 1 or 2.

R^4 , R^5 and R^6 all or independently represent a hydrogen atom or a C_1-C_6 alkyl radical as well as their salts of inorganic or organic bases, provided that that in the case of bis-gluconic acid amides

a) R^1, R^2, R^3, and R^4 do not simultaneously represent hydrogen atoms and that

b) when R^2 is a radical of formula II, and R^1, R^3 and R^4 are hydrogen atoms, A is not - $(CH_2)_2$-, and that

c) when R^2 is a radical of formula VI, in which m = 0, 1, 2, 3, or 5, and R^1, R^3 and R^4 are all hydrogen atoms and A is an unsubstituted straight-chain alkylene radical, the number of chain members is an odd number.

2. The compounds of claim 1, characterized by the fact that R^2 and R^3 are hydrogen.

3. The compounds of claim 2, characterized by the fact that R^1 represents radical III or radical VI, and m = 0.

4. The compounds of claim 1, characterized by the fact that R^1 and R^3 are hydrogen.

5. The compounds of claim 4, characterized by the fact that R^2 represents radical II or radical VI, and m = 0 or radical VII, and m = 0.

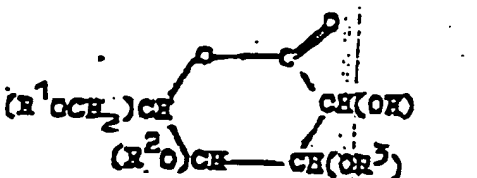
6. The compounds of claims 2 through 5, characterized by the fact that A in formula I represents a polymethylene radical - $(CH_2)_p$, and p = 2 to 22.

7. The compounds of claims 2 through 6, characterized by the fact that A in formula I represents a polymethylene radical - $(CH_2)_p$, and p = 2 to 12.

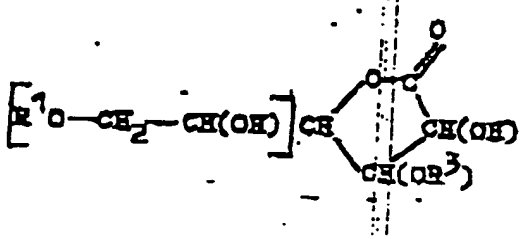
8. The compounds of claims 2 through 5, characterized by the fact that A in formula I represents a straight-chain alkylene radical having 2 to 22 carbon atoms, whose chain can be interrupted by the groups – 0- , - S -, - S - S -, - S - $(O)_n$, - C(=O)-NH- and/or - NR^6 -, where n and R^6 have the meanings defined in claim 1.

9. The compounds of claims 6 through 8, characterized by the fact that A in formula I is substituted by one, two or more radicals of – CO_2R^5, where R^5 has the meaning defined in claim 1.

10. A process for the preparation of bis-aldonamides of formula I as claimed in claim 1, characterized by the fact that an aldonolactone of formulae VIII or IX



(VIII)



(IX)

is reacted with a diamino compound of the formula $R^4HN–A-NHR^4$, wherein R^4 and A have the mannings defined in claim 1.

11. The process of claim 12, characterized by the fact that the aldonolactone of formulae VIII and IX are prepared in situ by eliminating water from the corresponding aldonic acids of formula X

$$R^1O—CH_2—CH(OH)—CH(OR^2)—CH(OR^3)—CH(OH)—CO_2H \quad (X)$$

and are reacted with the diamino compound without being isolated.